### Title

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### Journal

Nutrition reviews, 63(5)

### ISSN

0029-6643



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### Publication Date

2005-05-01

### DOI

10.1301/nr.2005.may.133-157

Peer reviewed

Lead Review Article

May 2005: 133–157

# Dietary Fructose: Implications for Dysregulation of Energy Homeostasis and Lipid/Carbohydrate Metabolism

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*Fructose intake and the prevalence of obesity have both increased over the past two to three decades. Compared with glucose, the hepatic metabolism of fructose favors lipogenesis, which may contribute to hyperlipidemia and obesity. Fructose does not increase insulin and leptin or suppress ghrelin, which suggests an endocrine mechanism by which it induces a positive energy balance. This review examines the available data on the effects of dietary fructose on energy homeostasis and lipid/carbohydrate metabolism. Recent publications, studies in human subjects, and areas in which additional research is needed are emphasized.*

Key words: obesity, diabetes, cardiovascular disease, triglycerides, leptin



doi: 10.1301/nr.2005.may.133–157

## INTRODUCTION

Recent review articles have focused on increased intake of dietary fructose and its possible association with the increased prevalence of obesity and obesity-related diseases over past two to three decades.[1,2] Potential metabolic and endocrine mechanisms underlying the effects of fructose consumption on energy balance and its relationship to weight gain and obesity have been proposed. Compared with other carbohydrates, which are composed primarily of glucose, the hepatic metabolism of fructose favors lipogenesis, which in addition to inducing hyperlipidemia, may contribute to weight gain and obesity. Furthermore, there are distinct differences between the effects of fructose and glucose on the secretion of insulin, leptin, and ghrelin, which are key signals involved in the long-term endocrine regulation of energy balance and body adiposity.[3,4]

Despite a number of studies demonstrating that fructose feeding leads to weight gain and hyperlipidemia in animals, and the epidemiological parallel between fructose intake and the marked increase in the proportion of overweight and obesity, there is currently little in the way of direct evidence linking these phenomena in humans. The goal of this review is to examine the currently available data on the interaction of dietary fructose with the endocrine and metabolic pathways involved in the control of energy homeostasis and lipid metabolism, emphasizing recently published studies and reviews and studies conducted in humans. Areas in which further research is needed are also discussed.

## SOURCES AND INTAKE OF DIETARY CARBOHYDRATE

### Dietary Carbohydrate Intake

The National Academy of Sciences has recommended that between 45% and 65% of energy be derived from carbohydrates, 20% to 35% from fat, and 10% to 35% from protein, with no more than 25% of total energy from added sugars.[5] Recommendations by the American Heart Association[6] and the American Diabetes Association[7] fall well within these broad guidelines: approximately 50% of energy from carbohydrate, 30% from fat, and 20% from protein. There are two major, population-based methodological approaches for estimating energy and nutrient intakes. Food disappearance data reflect the nationwide availability of foods and thus tend to overestimate consumption. In contrast, survey-based approaches that rely primarily on the ability of respondents to recall categories and amounts of previous intake tend to underestimate consumption but have the advantage of estimating intake characteristics in distinct subsets of the population. Results from the US Department of Agriculture Continuing Survey of Food Intakes by Individuals (CSFII) suggest that from 1994 to 1996, non-vegetarians

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Supported by a grant from the Academic Network, Portland, Oregon.

consumed 50% of energy from carbohydrate, 33% from fat, and 16% from protein, with 15% to 16% of energy provided by added sugars. Data from the National Health and Nutrition Survey (NHANES) as reported by the Centers for Disease Control and Prevention (CDC)[8] indicate that carbohydrate intake increased by about 62 g/d in women and by about 69 g/d in men between 1971 and 2000.

## Added Sugar and Fructose Intake

In a detailed report published in 2003[9] defining and interpreting the intake of sugars, the authors concluded that there is sufficient lack of rigor in data collection for added sugar intake to indicate that such estimates are likely to be inaccurate. Recent reviews cite the average per capita intake of added sugars from all sources based on economic disappearance data (i.e., available supply) to be approximately 64 kg per year in 1970 and approximately 80 kg per year (218 g/d; 872 kcal/d) in 2000, representing a 25% increase of added sweeteners over the past three decades.[1,2] These disappearance data most certainly overestimate total consumption, but not necessarily the proportional increase of added sugar intake. Survey-based intake data from the 1994–1996 CSFII, as analyzed by Bowman in 1999,[10] indicated an average per capita intake of added sugars of 79 g/d (316 kcal/d or 28.8 kg/year). This is certainly an underestimate of actual consumption. Of interest in these analyses are the top tertile of consumers, who derive about 27% of their calories from added sugars, with an average intake of 137 g/d (548 kcal),[10] and the top quintile of consumers averaging 178 g/d (712 kcal/d).[1]

Although free fructose, along with free glucose and sucrose, is present in significant quantities in fruits and some vegetables, the largest single source of fructose in the diet is added sugars consumed in desserts, candies, and, most importantly, in soft drinks and other sweetened beverages. The 1994–1996 CSFII data indicate that soft drinks and fruit drinks provide about 43% of the calories from added sugars. Disappearance data indicate that the primary source of added sweeteners in the United States is high-fructose corn syrup (HFCS),[11] which is used to sweeten the majority of beverages containing added sugars.

There is a widespread misconception among the public, and even some nutrition professionals, that HFCS is composed entirely of fructose. However, the vast majority of HFCS used in the US food supply is a mixture of glucose and fructose, with the most commonly used formulations containing either 42% fructose (HFCS-42) or 55% fructose (HFCS-55).[12] In addition, an increasing number of beverages are sweetened with concentrated fruit juices such as apple and white grape juice. Interestingly, fruit juices vary widely in the amount of fructose they contain, with apple juice containing 65% of energy from fructose and orange juice only 40% to 45%. Thus, apple juice and some juice-sweetened beverages can contain more fructose on a percent-energy basis than soft drinks sweetened with HFCS-42 or HFCS-55. Crystalline fructose of close to 100% purity is used to sweeten some beverages and foods.[13] While it is not clear precisely how much crystalline fructose is currently used in the food supply, its contribution to total fructose intake compared with sucrose and HFCS would still appear to be quite limited.

The replacement of sucrose with HFCS in soft drinks can impact the ratio of fructose to glucose in the diets of individuals, as HFCS-55 has a fructose-to-glucose ratio of 1.22 and contains 10% more fructose by weight than sucrose. Approximately 60% of the HFCS used in the food supply is HFCS-55 and 40% is HFCS-42.[11] It appears from the combined use of sucrose, HFCS-42, and HFCS-55 that fructose constitutes very close to 50% of energy in added sweeteners.[1] Therefore, 50% of the intake of added sweeteners discussed above is likely to provide a reasonably close approximation of total fructose intake. Accordingly, a conservative estimate based on CSFII survey data is that the average energy intake of fructose from added sugars is 7% to 8%. Energy from added sugars plus the naturally occurring sugars in fruit and fruit juices is over 12%. This estimate is based on consumption of sweets/desserts, soft drinks, fruit, and fruit juices.[14] Food disappearance data indicate that about 10% of the energy in the food supply is from fructose contained in added sugars. This is quite close to the 11.5% of energy value in the CFSII data from 1994–1998.

Thus, based on a 2000 kcal/d diet, average daily fructose consumption would be approximately 60 g/d. Again, these values are likely to underestimate actual consumption due to selective underreporting of specific foods and beverages.[15] Because some age groups, such as adolescent males, are heavy consumers of soft drinks,[16] and the top quintile of sugar users consume 2.2 times the average intake,[1] certain segments of the population are likely to be consuming well over 100 g/d of fructose from added sweeteners. For example, in one study of over 1400 8th-grade adolescents, 32.4% of their calorie intake was from added sugars, equivalent to 800 kcal/d (~200 g/d), of which approximately one-half or 400 kcal/d (100 g/d) would be expected to be derived from fructose.[17]

It is clear that whether disappearance data or survey results are used, total fructose intake, along with total energy and sweetener intake, has increased between the 1970s and the mid-1990s. The total amount of energy per capita available in the food supply based on food disap-

pearance data from the USDA increased by approximately 20% between 1975 and 2000, and total energy intake from NHANES survey data was reported to increase by 7% in men and 22% in women from 1971–1974 to 1999–2000.[8] Based on all available data, the increase of total per capita fructose consumption over these three decades is likely to be between 20% and 40%, with a 25% increase representing a reasonable estimate.

## SUGAR ABSORPTION

The principal sugars in the diet are glucose, fructose, sucrose, lactose, and maltose.[18] Maltose is a disaccharide composed of two molecules of glucose that are hydrolyzed at the intestinal brush border by maltases. Lactose is composed of one molecule of glucose and one molecule of galactose. After hydrolysis by lactase, galactose is converted to glucose in the process of absorption and transport by enterocytes. Thus, the majority of the carbohydrate in milk and dairy products is metabolized as glucose. Sucrose, which consists of one molecule of glucose and one molecule of fructose, is hydrolyzed by sucrase. Glucose, the product of starch (digested by amylases) and maltose digestion, is rapidly absorbed via a sodium-coupled co-transporter and arrives at the liver via the portal circulation.

Fructose absorption and transport through enterocytes to the portal bloodstream is performed by a fructose-specific hexose transporter, GLUT5, that is primarily expressed in the jejunum on both the brush border and the basolateral enterocyte membranes.[18] GLUT5 is also expressed, but at relatively lower levels, in kidney, skeletal muscle, adipocytes, and glial cells. Consumption of a large amount of pure fructose can exceed the capacity of intestinal fructose absorption, resulting in diarrhea. However, the consumption of glucose along with fructose, as it is usually consumed in beverages and with meals, appears to enhance fructose absorption.[19] In addition, fructose absorption increases during sustained fructose consumption, suggesting adaptation to increased fructose intake.

## FRUCTOSE METABOLISM

Although GLUT5 fructose transporters are expressed at low levels in a number of tissues, including skeletal muscle and adipose tissue, the liver is by far the most important site of fructose metabolism, which has important effects on both lipid and carbohydrate metabolism.[20] After absorption, ingested fructose arrives at the liver via the portal vein. The liver efficiently takes up portal fructose such that little escapes hepatic metabolism and enters the systemic circulation after consumption of moderate amounts of fructose. After ingestion of 1 g of fructose per kilogram body weight, blood fructose levels only increase to about 0.5 mmol/L. This is much less than the increase of plasma glucose levels (by ~10 mmol/L) in subjects with normal glucose tolerance after a 75 g oral glucose tolerance test. The half-life of fructose in the peripheral plasma after intravenous fructose administration in normal subjects is about 20 minutes.[21]

In the liver, fructose is phosphorylated by fructokinase to fructose-1-phosphate. Fructose-1-phosphate is then metabolized to triose phosphates, glyceraldehyde, and dihydroxyacetone phosphate. A portion of carbon derived from the triose phosphates can enter the gluconeogenic paythway and subsequently be released as glucose. Thus, a small but measurable increase of circulating glucose can be observed after fructose ingestion or intravenous infusion of fructose. A significant amount of fructose carbon entering glycolysis is metabolized to lactate and released, with smaller amounts released as pyruvate or alpha-ketoglutarate.[21] After ingestion of 45 g of fructose with a mixed meal, plasma lactate concentrations increased 3-fold (by ~2 mmol/L), whereas after the same amount of glucose, plasma lactate only increased by 0.5 mmol/L.[22] Presumably, a portion of this lactate is later taken up by the liver and enters gluconeogenesis to be converted to glucose or glycogen, or it can be metabolized to form acetyl-CoA.

A key aspect of hepatic fructose metabolism is that the entry of fructose via fructose-1-phosphate bypasses the main rate-controlling step in glycolysis, catalyzed by phosphofructokinase (Figure 1). In contrast, hepatic glucose metabolism is limited by the capacity of the liver to store glucose as glycogen and, more importantly, by the inhibition of glycolysis and further glucose uptake resulting from allosteric inhibition of phosphofructokinase by citrate and ATP (Figure 1). When large amounts of fructose are consumed, for example, in sucrose- or HFCS-sweetened beverages, significant quantities of fructose carbon continue to enter the glycolytic pathway distal to phosphofructokinase (Figure 1), facilitating very-low-density lipoprotein (VLDL) and triglyceride production in the liver. As the glycolytic pathway becomes saturated with intermediates, these can be converted to glycerol-3-phosphate, providing the glycerol moiety of triglyceride synthesis. They can also be further metabolized to pyruvate, and via pyruvate dehydrogenase to acetyl-CoA and citrate in mitochondria to provide carbon for de novo lipogenesis and to long-chain fatty acids that are then esterified to form triglycerides.[20]

Thus, unlike glucose metabolism, in which uptake is negatively regulated at the level of phosphofructokinase (Figure 1), high levels of fructose serve as an unregulated

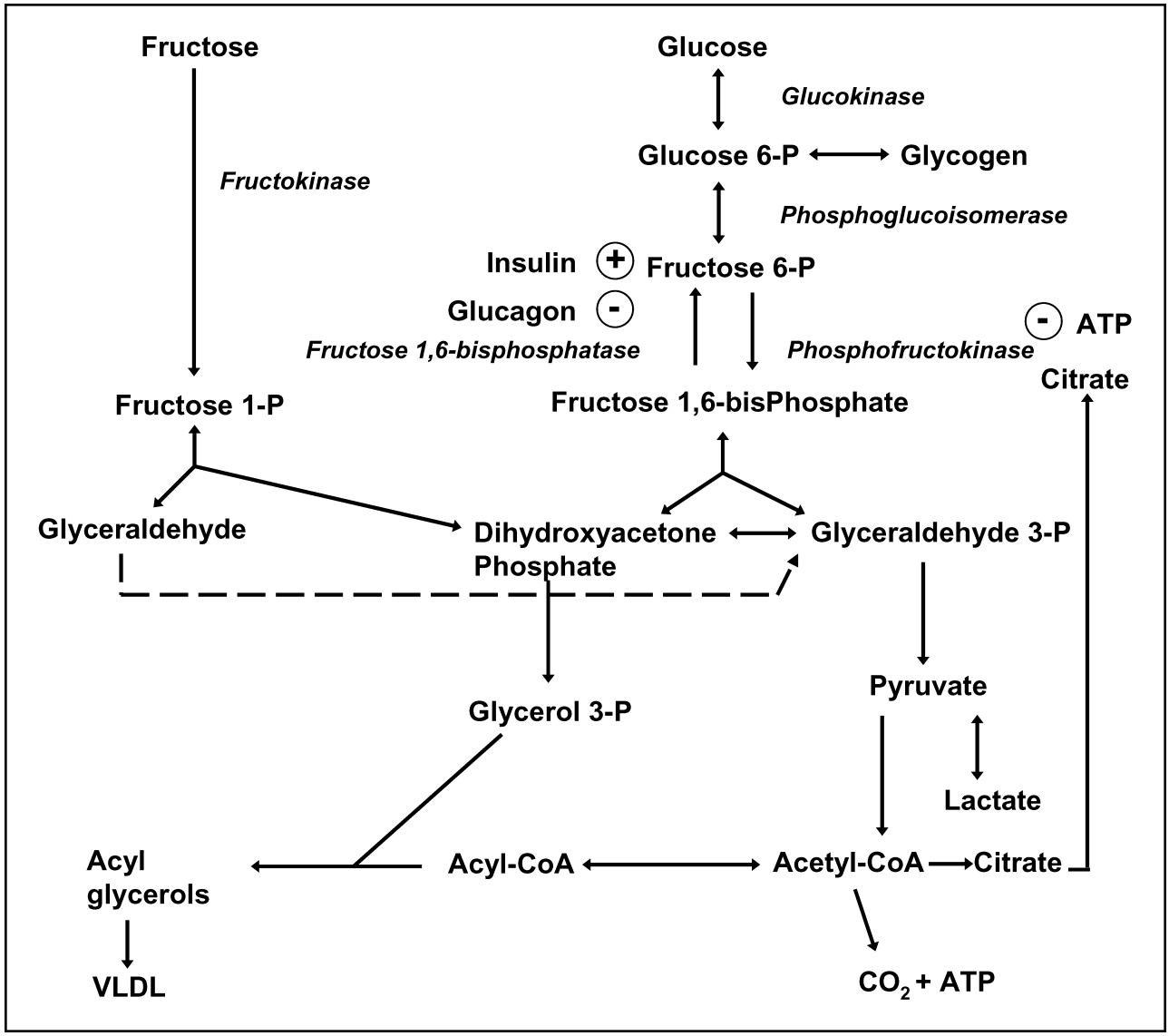


**Figure 1.** Fructose and glucose utilization in the liver. Hepatic fructose metabolism begins with phosphorylation by fructokinase. Fructose carbon enters the glycolytic pathway at the triose phosphate level (dihydroxyacetone phosphate and glyceraldehyde-3-phosphate). Thus, fructose bypasses the major control point (phosphofructokinase) at which glucose carbon enters the glycolytic pathway, which limits further glucose metabolism via feedback inhibition by citrate and ATP. These differences in the hepatic metabolism of fructose compared with glucose allow fructose to serve as an unregulated source of both glycerol-3-phosphate and acetyl-CoA, leading to enhanced lipogenesis.

source of hepatic acetyl-CoA production. While only a small percentage (1%–3%) of glucose carbon enters de novo lipogenesis and is incorporated into triglyceride in normal individuals, a proportionally much greater amount of carbon from ingested fructose is metabolized to triglyceride. Indeed, studies in human subjects have shown that fructose ingestion results in substantially increased rates of de novo lipogenesis,[23] which does not increase in response to eucaloric glucose ingestion.[24] Thus, fructose is more lipogenic than glucose, and this appears to be a major factor in its effects to induce hypertriglyceridemia in the postprandial state.

## FRUCTOSE AND LIPIDS

As discussed in the previous section, the hepatic metabolism of fructose favors lipogenesis, suggesting that fructose consumption could contribute to increases in circulating lipid levels. Recent reviews have examined the role of dietary carbohydrates in general,[25] and sugars in particular,[26] in triglyceride metabolism and cardiovascular disease risk. It is well known from studies in animals, including rodents,[27-30] dogs,[31] and nonhuman primates,[32] that feeding diets high in energy from fructose or sucrose induces hyperlipidemia.[2] It is the fructose

component of sucrose that is considered to increase triglyceride levels.[33]

In 1966, Macdonald[34] reported that feeding fructose but not glucose for 5 days increased serum triglycerides in men and postmenopausal but not premenopausal women. High-sucrose diets also elevated fasting triglyceride concentrations in humans, while consuming an equal amount of glucose resulted in lower serum triglyceride levels.[28] This effect of sucrose to raise triglycerides was dose dependent in hyperinsulinemic subjects.[35] In 1983, Hallfrisch et al.[36] reported that fasting total and LDL cholesterol were increased after 5 weeks in subjects consuming diets containing 15% energy from fructose, and plasma triglyceride concentrations increased in hyperinsulinemic subjects as the level of dietary fructose increased. Swanson et al.[37] reported that LDL cholesterol increased during a 4-week crossover study when normal subjects consumed a diet containing 20% energy as fructose, but not when the fructose was replaced with starch.[37] Increases of total and LDL cholesterol during 4 weeks of 20% fructose consumption have also been reported in subjects with diabetes.[38] In another study, fasting triglyceride and total cholesterol levels increased in both normal and hyperinsulinemic subjects when they consumed 20% energy from fructose but not from cornstarch; VLDL, LDL, and apolipoprotein B100 (ApoB100) were also significantly elevated in the hyperinsulinemic subjects.[39] In contrast, other investigators have not reported increases of fasting lipids in subjects with insulin resistance or diabetes when fructose was consumed at 13%,[40] 15%,[41] or 20%[42] of energy.

The inconsistent effects of fructose to induce hyperlipidemia may be dependent on the amount of fructose in the diet, on whether fasting or postprandial lipids are measured, and on the potential for gender differences in circulating lipid responses to fructose consumption. Postprandial measurements may detect changes in lipid profiles that are not detected in the fasting state.[43] Certainly the acute consumption of meals high in fructose or sucrose (50% fructose) can acutely increase postprandial triglyceride levels. For example, the addition of 50 g of fructose or 100 g of sucrose to a 40-g fat meal increased postprandial triglyceride levels over 7 hours, whereas consumption of 50 g of glucose with the meal had no effect on the triglyceride response.[44] In a 12-week crossover study, Bantle et al.[45] compared the effects of 6 weeks of fructose or glucose consumption (17% of energy) on both fasting and postprandial lipid levels in normal-weight men and women. Fasting triglyceride concentrations decreased by approximately 30% over pre-study levels in men when glucose was consumed, but were unchanged during the fructose diet. Neither glucose nor fructose affected fasting triglyceride levels in women. In addition, day-long plasma triglyceride levels were elevated by 30% in men consuming fructose compared with glucose; however, postprandial triglycerides were not different between the glucose and fructose diets in women.

In a recently published study, the short-term effects of consuming fructose- and glucose-sweetened beverages (providing 30% of total energy) consumed with three meals over a 24-hour period were compared in 12 normal-weight young women with normal fasting triglyceride levels.[22] In this crossover study, plasma triglyceride concentrations increased more rapidly and peaked at higher levels after the consumption of fructose-containing beverages compared with those containing glucose. Plasma triglyceride concentrations remained elevated after fructose consumption, but declined below fasting levels several hours after glucose consumption. Net triglyceride exposure as assessed by the area under the curve above fasting levels was not increased when glucose beverages were consumed, but the area under the curve was highly positive and total triglyceride exposure was increased by over 20% above fasting levels on the day fructose-sweetened beverages were consumed.

In a long-term (10-week) study, the effects of consuming diets containing 25% of energy as fructose or glucose on postprandial triglyceride profiles were examined in overweight women with normal triglyceride levels.[46] A progressive increase in postprandial triglyceride concentrations (compared with a baseline complex carbohydrate diet) was observed over 14 hours in subjects consuming fructose-sweetened beverages with meals, and the effect was much more pronounced after 10 weeks than after 2 weeks of fructose consumption. In contrast, postprandial triglyceride profiles were not increased after 2 or 10 weeks in subjects randomized to consume glucose-sweetened beverages with meals, despite substantially larger plasma insulin and glucose excursions when glucose was consumed compared with the baseline complex carbohydrate diet. In addition, postprandial ApoB levels increased by approximately 12% after 10 weeks in subjects consuming the high-fructose diet but not in those subjects on the high-glucose diet.[46] Postprandial triglyceride profiles were also elevated in rhesus monkeys after one year of consuming a high-fructose diet, but not in animals after one year on a high-glucose diet (P. Havel, unpublished data), indicating that the hyperlipidemic effects of consuming fructose are persistent.

## MECHANISMS AND ATHEROGENICITY OF FRUCTOSE-INDUCED HYPERLIPIDEMIA

Elevated triglyceride levels reflect an imbalance between the rates of VLDL-triglyceride production and clearance. A major factor influencing hepatic triglyceride secretion

**Table 1.** Effects of Fructose or Sucrose Consumption on Circulating Lipids in Human Subjects

| Subjects | Amount Fed | Length of Study | Observed Effects |
|---|---|---|---|
| Healthy young male ($n$ = 5), premenopausal female ($n$ = 6), and postmenopausal female subjects ($n$ = 3) (Macdonald, 1966)[34] | Fat-free diet containing 50 g casein and 7.7 g/kg body weight of 40% glucose or fructose | 5 days | Serum triglycerides were increased by 50% in men and 90% in postmenopausal women, but not in premenopausal women during fructose compared with glucose consumption |
| Normal male subjects (Herman, 1970)[28] | 20%–80% of energy from sucrose/glucose in a 3000 kcal/day liquid diet | 3 weeks each | Increased TG when subjects were fed sucrose compared with glucose |
| Hyperinsulinemic male ($n$ = 12) and female ($n$ = 12) subjects (Reiser, 1981)[35] | Sucrose at 5%, 18%, and 33% of energy. | 6 weeks | Dose-dependent increases of fasting TG and total, VLDL, and LDL cholesterol in male but not female subjects |
| Male subjects with normal insulin levels ($n$ = 12) and male subjects with hyperinsulinemia ($n$ = 12) (Hallfrisch, 1983)[36] | Diets with 0%, 7.5%, and 15% of energy from fructose; crossover design | 5 weeks at each level | Plasma TG increased by 30% and 60% after 5 weeks of fructose 7.5% and 15% energy in hyperinsulinemic men but was unchanged in normal men |
| Healthy subjects ($n$ = 14) (Swanson, 1992)[37] | 20% energy from fructose or starch; crossover design | 4 weeks each | Fasting total and LDL cholesterol increased by 9% and 11% by fructose compared with starch; transient increase of postprandial TG |
| Subjects with type 1 ($n$ = 6) and type 2 ($n$ = 12) diabetes (Bantle, 1992)[38] | 20% energy from fructose or starch; crossover design | 4 weeks each | Fasting total and LDL cholesterol increased by 7% and 11% with fructose compared with starch; no changes in HDL, fasting, or postprandial TG |
| Male subjects with normal insulin levels ($n$ = 10) and male subjects with hyperinsulinemia ($n$ = 11) (Reiser, 1989)[39] | 20% energy from fructose or starch; crossover design | 5 weeks each | Increased TG and total and VLDL cholesterol in all subjects; increased ApoB, ApoCII, and ApoCIII in hyperinsulinemic subjects |
| Subjects with type 2 diabetes ($n$ = 5) (Thorburn, 1989)[40] | 13% of energy from fructose | 12 weeks | No changes in total or LDL cholesterol or VLDL production rates from 3H-2-glycerol |

**Table 1.** Effects of Fructose or Sucrose Consumption on Circulating Lipids in Human Subjects (Cont'd)

| Subjects | Amount Fed | Length of Study | Observed Effects |
|---|---|---|---|
| Subjects with type 2 diabetes ($n$ = 9) (Osei, 1987)[41] | 60 g/day of fructose (~12% of energy @ 2000 kcal/day) | 12 weeks | No changes of fasting TG or total, LDL, or HDL cholesterol |
| Six subjects with elevated TG (2 had diabetes) (Turner, 1979)[42] | Liquid diets with 20% energy from fructose | 2 weeks | No change in TG levels |
| Normal weight male ($n$ = 9) and female ($n$ = 12) subjects (Cohen, 1988)[44] | 50 g fructose, sucrose, or glucose, 100 g sucrose with a 40-g fat "meal" | 7 hours postprandial | Increased postprandial TG responses with 50 g fructose or 100 g sucrose, but not with 50 g sucrose or 50 g glucose |
| Healthy non-obese male ($n$ = 12) and female ($n$ = 12) subjects (Bantle, 2000)[45] | 17% of energy as either fructose or glucose; crossover design | 6 weeks | Higher fasting and 32% greater postprandial TG responses with fructose compared with glucose in men but not women; no effects on fasting total, LDL, or HDL cholesterol |
| Healthy non-obese female subjects ($n$ = 12) (Teff, 2004)[22] | Meals with 30% of energy as either fructose or glucose as beverages | 24 hours each | Higher postprandial TG responses after fructose than glucose beverages |
| Overweight/obese women ($n$ = 11) (Havel, 2003)[46] | Meals with beverages containing 25% of energy from glucose or fructose | 10 weeks | Increased postprandial TG responses and ApoB levels after 10 weeks of fructose but not glucose consumption |
| Subjects with type 2 diabetes ($n$ = 7) (Crapo, 1986)[51] | Mixed meals containing 20% of energy as fructose or sucrose | 2 weeks | 13% increase of fasting TG in the 5 subjects with initial TG $<$ 150 mg/dL. |
| Healthy subjects ($n$ = 11) (Jeppesen, 1995)[52] | Fat meal (40 g) $\pm$ 50 g fructose | 10-hour acute study | Increased postprandial TG with fructose; response proportionate to fasting TG |
| Normal subjects ($n$ = 6) and subjects with type 2 diabetes ($n$ = 6) (Abraha, 1998)[53] | Fructose or starch (0.75 g/kg body weight) | 6 h postprandial study | Increased postprandial TG response to fructose compared with starch in all subjects; increase of TG positively related to fasting insulin levels |
| Subjects with type 2 diabetes (n = 10) (Koivisto, 1993)[105] | Mixed-meal diet with 20% of energy as fructose or starch | 4 weeks | No change of fasting TG levels |

TG = triglycerides.

is fatty acid availability.[47] Hepatic de novo lipogenesis can increase fatty acid availability by two processes: 1) by the direct effect of de novo fatty acid synthesis, and 2) indirectly as the result of increased levels of hepatic malonyl-CoA, which potently inhibits fatty acid oxidation by blocking fatty acid transport into the mitochondria via carnitine palmitoyltransferase-1.[48,49] Both mechanisms lead to increased esterification/re-esterification of fatty acids and increased hepatic triglyceride synthesis that in turn leads to increased circulating VLDL-triglyceride levels

Acetyl CoA is the principal component of fatty acids produced by de novo lipogenesis[24] and, as previously discussed, high levels of dietary fructose serve as an unregulated source of hepatic acetyl-CoA production. Fractional hepatic de novo lipogenesis is dramatically increased during fructose ingestion compared with glucose ingestion,[23] and it has been reported that nearly 30% of circulating palmitate in triglycerides after fructose ingestion is from fructose-derived de novo lipogenesis.[50] In contrast, Hellerstein[24] has shown that there is little de novo lipogenesis from glucose under eucaloric conditions in humans. There is evidence that the effect of fructose in increasing postprandial triglyceride levels is exacerbated in subjects with existing hypertriglyceridemia[51,52] or insulin resistance.[53] Therefore, chronic hyperinsulinemia and increased circulating fatty acids, which are commonly seen with central obesity and insulin resistance, may further increase hepatic de novo lipogenesis during fructose consumption in subjects with metabolic syndrome.

Several studies conducted in rodents have investigated the mechanisms by which fructose contributes to increased triglyceride levels. One study in rats fed 70% fructose or glucose diets indicated that fructose may increase de novo lipogenesis by increasing substrate flux through pyruvate dehydrogenase via inhibition of pyruvate dehydrogenase kinase.[54] Taghibiglou et al.[55] investigated mechanisms for the overproduction of VLDL in an insulin-resistant, fructose-fed hamster model (60% energy from fructose), and found evidence for enhanced lipoprotein assembly, reduced intracellular ApoB degradation, and increased hepatic expression of microsomal triglyceride transfer protein. Together, these findings help explain the increased assembly and secretion of ApoB-containing lipoproteins in fructose-fed animals.[55] It is also possible that reduced triglyceride clearance could contribute to fructose-induced hypertriglyceridemia.

A study in rats suggested that fructose reduced VLDL-triglyceride removal by lowering the ApoE to ApoC ratio.[56] In addition, the reduced postprandial insulin responses to high-fructose meals[22] could lead to less activation of lipoprotein lipase and decreased triglyceride removal via this mechanism. The reports that ApoB levels increase during fructose consumption[39,46] suggest that increases of VLDL-triglyceride represent a significant component of fructose-induced increases of postprandial triglycerides. New studies are needed to definitively determine the relative contributions of increased production and decreased clearance of VLDL-triglyceride to the hyperlipidemic effects of fructose consumption.

In summary, several short-term studies have implicated fructose in promoting unfavorable lipid profiles. Both short-term and long-term fructose consumption increase postprandial triglyceride levels. In a preliminary study, the hypertriglyceridemic effects of fructose were more pronounced after 10 weeks than 2 weeks, and fructose consumption also increased postprandial levels of atherogenic ApoB.[46] High triglyceride levels are an independent risk factor for coronary heart disease.[57,58] This understanding is based largely on evidence meta-analyses of population-based studies.[59-61] Moderate increases of VLDL-triglyceride are associated with other lipoprotein changes, including reduced HDL[62,63] and small, dense LDL,[64,65] which are components of the metabolic syndrome and are recognized as risk factors for atherosclerotic disease.

Our unpublished data demonstrate a strong correlation between the observed increases in postprandial triglycerides and ApoB after 10 weeks of high fructose consumption. Atherogenic risk is strongly dependent upon plasma lipoproteins containing ApoB100,[66] which facilitates the accumulation of cholesterol and other lipids into the arterial wall by multiple mechanisms.[67,68] Although consumption of fructose can increase triglycerides and ApoB, the effects of fructose consumption on other potential markers and mediators of atherogenesis and/or inflammation, such as small, dense LDL, remnant lipoproteins, interleukin-6, C-reactive protein, and platelet activator inhibitor-1, have not been investigated.

## FRUCTOSE AND INSULIN RESISTANCE

Insulin resistance, along with visceral obesity, dyslipidemia, and hypertension, is a major component of the metabolic syndrome and is strongly associated with an increased risk for cardiovascular disease. When combined with impaired islet/$\beta$-cell function in genetically predisposed individuals, insulin resistance leads to type 2 diabetes. Feeding diets containing high levels of fructose impairs insulin action in animals. Feeding fructose or sucrose (50% fructose) to animals has often been employed to produce animal models of insulin resistance. Consumption of a high fructose diet for 4 weeks in rats induced systemic insulin resistance and reduced tyrosine phosphorylation of the insulin receptor in liver, as well as

impaired insulin-stimulated IRS-1 phosphorylation and IRS-1 association with phosphoinositol-3-kinase in both liver and skeletal muscle,[69] suggesting specific points in the insulin signal transduction pathway that are affected by dietary fructose. The effects of dietary sugars on insulin action in animals and humans have been examined in several recent reviews.[2,70-72] When compared with studies conducted in experimental animals, much more limited data are available concerning the effects of fructose consumption on insulin action in humans.

Accurate assessment of insulin sensitivity requires specific methods such as hyperinsulinemic clamps or fast-sampled intravenous glucose tolerance tests with mathematical modeling of insulin action. Without such methods, insulin sensitivity must be estimated by measuring fasting insulin levels or employing indices such as the homeostasis assessment model, which are derived from measurements of fasting insulin and glucose. However, while fasting insulin and derivations thereof are more suitable for larger epidemiological studies, generally these measurements lack the sensitivity required to assess insulin action in smaller-scale interventional experiments.

In 1980, Beck-Nielsen et al.[73] reported that overfeeding human subjects fructose at 1000 kcal/d was accompanied by reductions in insulin binding to monocytes in vitro and in whole-body insulin sensitivity as determined by an intravenous insulin tolerance test, whereas glucose overfeeding (also 1000 kcal/d) had no effects on insulin binding or insulin sensitivity. Hallfrisch et al.[74] reported that consumption of diets containing 15% of energy as fructose resulted in undesirable changes in glucose metabolism, as suggested by increased glucose and insulin responses to an oral sucrose load; these effects were more pronounced in hyperinsulinemic subjects. In contrast, results from several other studies did not demonstrate any measurable effects of fructose consumption on insulin action.[42,75,76] Similar discrepancies have been reported in studies in which fructose was provided as 50% of dietary sucrose.[77-79] Potential explanations for the discrepancies between human studies include the amount (dose) of the sugars included in the diet, the duration of dietary intervention, and the other components included in the background diet around which sugar content was manipulated. For example, if the intervention diet is low in fat, this might lessen the effects of the fructose component to impair insulin action. In addition, some studies compared the effects of dietary fructose with sucrose such that the comparison diet already contained half the amount of the fructose available in the intervention diet. Another important consideration is that normal-weight and/or insulin-sensitive subjects might be relatively resistant to the insulin-desensitizing effects of sustained fructose consumption, whereas fructose may be more likely to exacerbate insulin resistance in subjects with existing deficits in insulin action. Such differential sensitivity to the adverse effects of dietary fructose may be similar to the better-documented effects of fructose to further increase triglycerides in subjects with existing hypertriglyceridemia (as discussed above).

Although fructose does not directly stimulate insulin secretion, insulin secretion will increase, resulting in compensatory hyperinsulinemia, if long-term fructose consumption leads to obesity and insulin resistance. In addition, insulin resistance often coexists with increased levels of circulating fatty acids[80] and triglycerides,[81] which have been implicated in the etiology of insulin resistance.

Perhaps the most compelling link between lipid metabolism and insulin resistance is that both circulating free fatty acids and fatty acids derived from triglycerides, as well as those synthesized locally, can lead to ectopic fat deposition in liver and skeletal muscle. Liver triglyceride content and intramyocellular lipid content are closely linked to liver and muscle insulin resistance, respectively.[82-84] Thus, the lipogenic effects of fructose already discussed may contribute indirectly to insulin resistance via accumulation of fructose-derived lipids in liver and skeletal muscle during long-term overconsumption of fructose. High-fructose diets can increase hepatic triglyceride content in humans,[85] and the decreased export of triglycerides synthesized in the liver may contribute to this effect.[86] Fructose feeding in rats not only increases circulating triglyceride and free fatty acid concentrations,[40] but also leads to lipid deposition in liver and muscle,[87,88] which may contribute to the observed induction of insulin resistance. In addition, administration of the peroxisome proliferator-activated receptor-alpha (PPAR$\alpha$) agonist fenofibrate improves fructose-induced insulin resistance, in association with reductions of circulating triglyceride and free fatty acid concentrations and tissue triglyceride levels.[87,88] If ectopic fat deposition does indeed contribute to the development of fructose-induced insulin resistance, many of the previous studies investigating the effects of fructose on insulin action may have been too short in duration for liver and muscle triglycerides to accumulate to the extent that insulin action would be measurably compromised.

Reduction of hypertriglyceridemia induced with several pharmacological agents reverses the insulin resistance induced by fructose feeding in rats.[27,88,89] As previously discussed, postprandial hypertriglyceridemia after fructose ingestion is exacerbated in humans[53] and rhesus monkeys with high fasting insulin levels (unpublished observation), also suggesting an interaction between insulin resistance and the lipogenic effects of fructose. Hepatic gluconeogenic and lipogenic pathways

share common precursors and can be coordinately regulated. Prior studies have indicated that the normal liver can accommodate increased gluconeogenic precursor flux. However, when a large quantity of fructose, which is metabolized to gluconeogenic precursors such as lactate and pyruvate, is infused, both glucose production[90] and de novo lipogenesis[50] are increased. There is evidence for increased hepatic flux of gluconeogenic precursors in insulin-resistant subjects, and this has been suggested as a common mechanism underlying both hyperglycemia and hypertriglyceridemia.[91-93] In clamp studies utilizing tracer methodology, Dirlewanger et al.[94] demonstrated that intravenous fructose infusion acutely induced insulin resistance as determined by glucose clamp studies and increased hepatic glucose output. An impairment of glucose disappearance was also reported in this study, but the mechanism was not identified.

In summary, while it is clear that fructose feeding can induce insulin resistance and glucose intolerance in experimental animals (mainly rodents), few long-term studies have been conducted in humans. The potential mechanisms involved in fructose-induced insulin resistance include direct effect on insulin signaling, direct effects on hepatic glucose production, and indirect effects resulting from hepatic and muscle lipid accumulation. It is possible that these mechanisms have additive or synergistic effects in the induction of insulin resistance. Because it is evident that fructose consumption has increased significantly, new studies are needed to systematically investigate the long-term effects of fructose on insulin action and glucose tolerance, particularly in hypertriglyceridemic individuals with hyperinsulinemia who are at increased risk for cardiovascular disease. It is important in such studies to employ appropriate methods to assess insulin sensitivity and to determine the effects of fructose on hepatic glucose metabolism, as well as hepatic and intramyocellular lipid accumulation.

## FRUCTOSE AND DIABETES

Smith et al.[21] were among the first to investigate the metabolism of fructose in subjects with diabetes mellitus, reporting that the half-life of fructose was prolonged and that urinary glucose excretion after fructose infusion was greater in diabetic than in normal subjects, suggesting that the conversion of fructose to glucose is increased in diabetes. This may be the result of higher rates of gluconeogenesis from lactate and pyruvate generated from fructose in subjects with diabetes. The role of dietary carbohydrates, and sugars in particular, in the nutritional management of diabetes mellitus has recently been reviewed in detail.[95] In the past, fructose has been recommended as a dietary sweetener in the nutritional management of diabetes because it reduces postprandial hyperglycemia compared with sucrose. Fructose ingestion also results in smaller postprandial glucose excursions compared with the ingestion of glucose and glucose-containing carbohydrates (starches), which are rapidly absorbed as glucose.[22,96]

Infusion of small amounts of fructose into the portal vein increases hepatic uptake of glucose,[97] an effect that may be mediated by induction of hepatic glucokinase. Small quantities of fructose also increase carbon flux through glycogen synthase, stimulate glycogen synthesis,[98] and restore the ability of hyperglycemia to regulate hepatic glucose production in humans.[99] Thus, small quantities of fructose appear to have a "catalytic" effect to improve hepatic glucose uptake and storage as glycogen, perhaps as a consequence of activation of hepatic glucokinase.[98,100] The addition of 7.5 g of fructose to a 75-g oral glucose tolerance test reduced the glycemic response in adults with type 2 diabetes,[101] suggesting that limited amounts of oral fructose would be useful in improving glycemic control in type 2 diabetes.

Several studies have demonstrated that the addition of small to moderate amounts of fructose or sucrose to the diet has no deleterious effects, and even some beneficial effects, on glucose metabolism in subjects with type 2 diabetes.[41,102-106] For example, Osei et al.[107] fed 60 g/d of fructose (~10%–15% of energy) with isocaloric weight-maintaining diets to 13 patients with poorly controlled type 2 diabetes for 6 months in a crossover study with the control diet providing mainly complex carbohydrate. Fasting glucose decreased from 227 to 176 mg/dL and glycosylated hemoglobin decreased from 11.3% to 9.9%.[107] Using more sophisticated approaches for assessing glucose metabolism (hyperinsulinemic euglycemic clamps), Thorburn et al.[108] reported that after 3 months on a diet providing 13% of energy as fructose to subjects with type 2 diabetes, hepatic glucose production, hepatic insulin sensitivity (insulin-mediated suppression of endogenous glucose production), and peripheral glucose disposal were all unchanged. Unfortunately, because the baseline comparison diet in this study contained 13% sucrose, the incremental difference of fructose intake on the higher-fructose diet was only 6.5% of energy consumed. Nonetheless, most studies conducted to date have not demonstrated adverse effects on consuming moderate amounts of fructose on glycemic control or insulin sensitivity in patients with type 2 diabetes during periods of neutral energy balance.

Of greater concern, however, is the potential impact of consuming large amounts of fructose on lipid metabolism in subjects with type 2 diabetes, who are at a substantially increased risk of cardiovascular disease. A number of studies examining the effects of dietary fructose in patients with type 2 diabetes have not reported increases of fasting lipids.[41,103] Osei et al.[107] found no

**Table 2.** Effects of Fructose or Sucrose Consumption on Parameters of Insulin Resistance/Glucose Metabolism in Human Subjects

| Subjects | Amount Fed | Length of Study | Observed Effects |
|---|---|---|---|
| Male and female subjects (Beck-Nielsen, 1980)[73] | 4.18 MJ (1,000 extra kcal) as fructose or glucose | 7 days | Reducted insulin binding to monocytes in vitro and reduced insulin sensitivity (IV insulin tolerance test) with fructose; no effects with glucose over-feeding |
| Male subjects with normal insulin levels ($n = 12$) and male subjects with hyperinsulinemia ($n = 12$) (Hallfrisch, 1983)[74] | Diets with 0%, 7.5% and 15% of energy from fructose; crossover design | 5 weeks each | Increased insulin and glucose responses to an oral sucrose load on the 15% fructose diet compared with the other two diets |
| Subjects with elevated TG ($n = 6$) (2 had diabetes) (Turner, 1979)[42] | Liquid diets with 20% energy from fructose | 2 weeks | No changes in fasting glucose or insulin or glucose and insulin responses to a formula meal tolerance test |
| Nonobese adolescent children ($n = 12$) (Sunehag, 2002)[76] | Mixed macronutrient diet with 10% or 40% energy from fructose | 7 days | No effects on fasting insulin levels or insulin sensitivity measured with an IV glucose tolerance test |
| Male ($n = 10$) and female ($n = 9$) subjects (Reiser, 1979)[77] | Mixed meals with 30% of energy as sucrose in exchange for starch; crossover design | 6 weeks | Increased fasting glucose and insulin levels and insulin responses to an oral sucrose load |
| Male ($n = 12$) and female ($n = 12$) subjects with exaggerated insulin responses to oral sucrose (Reiser, 1981)[78] | Mixed diets containing 6%, 18%, or 33% energy from sucrose; crossover design | 6 weeks | Time-dependent increases of fasting insulin levels and insulin responses to an oral sucrose load |
| Healthy adult subjects ($n = 8$) (Daly, 1998)[79] | Mixed meals with 50% energy as starch or sucrose; crossover design | 24 hours each | No acute effects of the sucrose diet as assessed by an IV insulin tolerance test performed at 24 hours |
| Subjects with type 2 diabetes ($n = 10$) (Koivisto, 1993)[105] | Mixed-meal diet with 20% of energy as fructose or starch | 4 weeks | No changes of fasting insulin or insulin responses to an oral glucose tolerance test, but fasting glucose and HbA1c decreased and insulin sensitivity (euglycemic clamp) was improved during fructose consumption |

increase of fasting cholesterol, triglycerides, or ApoA1 or ApoB100 in type 2 diabetic subjects after six months on a diet providing 60 g of fructose per day. Thorburn et al.[40] also reported no deleterious changes of lipid metabolism, including free fatty acids, total cholesterol, LDL, or VLDL production rates assessed by labeled glycerol incorporation into triglyceride, when comparing 13% fructose with 13% sucrose diets. However, in another study by the same investigators, a 20% fructose diet did increase triglyceride levels after 2 weeks in diabetic subjects with higher baseline fasting hypertriglyceride levels (>150 mg/dL).[51] In another study employing a 20% fructose diet in diabetic subjects, total and LDL cholesterol were increased by 7% and 11%, respectively, after 4 weeks.[38] Thus, the existing data regarding the effects of moderate amounts of dietary fructose on lipids in subjects with type 2 diabetes are equivocal. Given the more extensive and more recent data demonstrating adverse effects of fructose consumption on lipids, particularly postprandial triglyceride and ApoB levels, new studies are needed to investigate the effects of fructose consumption in this at-risk population. Of particular interest is the impact of dietary fructose when it is consumed in combination with high-fat meals in a setting of positive energy balance rather than in the setting of neutral energy balance (eucaloric feeding) employed in most clinical nutrition studies.

There are other potential concerns regarding fructose consumption in patients with type 2 diabetes. Compared with glucose, fructose ingestion only weakly stimulates insulin secretion. In addition to insulin's involvement in the long-term regulation of energy balance, augmentation of insulin secretion is an important goal of diabetes therapy, particularly since the early insulin response to meals is an important determinant of postprandial glucose control.[109-111] In addition, the lack of effects of dietary fructose on the endocrine signals involved in the long-term regulation of energy balance discussed in the following section suggests that prolonged consumption of a high-fructose diet, along with dietary fat and inactivity, could contribute to weight gain and therefore worsen insulin resistance and other risk factors for cardiovascular disease.

Finally, little is known regarding the effects of fructose on diabetic complications, specifically the potential impact of fructose to contribute to protein fructosylation[112] and oxidative stress.[113] Significant amounts of fructose may escape hepatic uptake, resulting in increased systemic circulating fructose concentrations after consumption of large quantities of fructose (e.g., sweetened beverages). Fructose is a major product of the polyol/sorbitol pathway, and tissue fructose accumulation has been implicated in diabetic neuropathy and other complications of diabetes.[114-116] These complications could reflect increases of protein fructosylation. In a recent study, a diet providing 40% of energy from fructose increased both the formation of cataracts and oxidative by-products in the kidneys of streptozotocin diabetic rats compared with a high-glucose control diet.[117] Increased glycation (fructosamine and glycated hemoglobin) and markers of lipid peroxidation and aging have been observed in rats consuming a high-fructose diet compared with animals consuming a high-glucose diet.[118] Fructose feeding decreases antioxidant defense systems,[119,120] and oxidative stress has been implicated as a contributing factor in insulin resistance and impaired beta-cell function.[121,122] In contrast, one long-term study in non-diabetic rats consuming fructose, glucose, sucrose, or starch as the sole source of dietary carbohydrate found no differences in levels of advanced glycation end-products in collagen.[123] It is not known whether glycation and oxidation-related products are increased and could contribute to diabetic complications in humans with type 2 diabetes who consume high levels of dietary fructose.

In summary, existing data from short-term studies indicate that small to moderate amounts of dietary fructose do not adversely impact, and may even improve, glycemic control in patients with type 2 diabetes. Some, but not all, studies suggest the potential for undesirable effects of fructose consumption on lipid metabolism in type 2 diabetes. Patients with existing hyperlipidemia may be at increased risk for fructose-induced dyslipidemia. The potential for sustained consumption of a diet high in fructose to contribute to weight gain and diabetic complications is also a concern. New studies are needed to investigate the long-term metabolic impact of fructose in diabetes.

## FRUCTOSE, ENERGY HOMEOSTASIS, AND OBESITY

### Short-term versus Long-term Regulation of Energy Homeostasis

Body weight and adiposity are tightly regulated over relatively long periods of time. Even after large alterations of body fat resulting from restriction of energy intake or overfeeding, body weight and fat stores tend to return to pre-intervention levels when ad libitum feeding resumes.[124,125] Food intake, energy expenditure, and body fat stores are regulated by a variety of nutrient, endocrine, and neural signals originating in the periphery and providing information to the central nervous system centers in the hindbrain and hypothalamus that coordinate energy homeostasis.[3] Food intake and energy balance are regulated by distinct, but interacting, short-term and long-term mechanisms. Incoming nutrients, disten-

sion of the stomach and upper intestine, as well as a number of hormones produced by the gut, including cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1), act as short-term signals of satiety that limit meal duration and meal size. However, these short-term signals are not, by themselves, able to regulate body adiposity in the long term.

Other long-term endocrine regulators of energy homeostasis are released in proportion not only to body fat stores, but also to the quantity and macronutrient composition of food consumed over more prolonged periods. Insulin secreted by the endocrine pancreas, leptin produced by adipocytes, ghrelin from the stomach, and possibly peptide $YY_{3-36}$ ($PYY_{3-36}$) from the distal intestine appear to be involved in the long-term regulation of energy balance and body adiposity (Figure 2). Changes in the production and circulating levels of these hormones help to ensure that appetite, food intake, and metabolic rate are appropriately modified in order to maintain body weight/fat stores in energy balance. Adjustments in the production of long-term hormonal signals appear to function as determinants of the effectiveness of the short-term signals to decrease meal size and duration. For example, following a period of energy restriction during which insulin secretion and leptin production are diminished and circulating ghrelin levels are increased, a larger extent of gastrointestinal distension and greater CCK and GLP-1 release are required to signal satiety to the CNS and induce cessation of eating.[126-128] In the next sections, the major long-term endocrine signals known to be involved in the regulation of energy homeostasis are reviewed and recent data examining the effects of fructose consumption on these hormones are discussed.

## Insulin

Insulin is involved in the regulation of body adiposity via its actions in the CNS to inhibit food intake and increase energy expenditure.[129,130] Insulin is secreted in response to the ingestion of glucose-containing carbohydrates and certain amino acids released from ingested protein, as well as cephalic phase activation of vagal neural input to the pancreas[131] and the gastrointestinal incretin hormones GIP and GLP-1.[132] Insulin receptors are highly expressed in several CNS areas involved in the control of food intake and energy homeostasis, including the hypothalamus. Direct administration of insulin into the CNS inhibits food intake in animals, including nonhuman primates. Genetic or antisense inactivation of insulin receptor function or administration of inhibitors of insulin signal transduction in the CNS results in increases of food intake and body adiposity in rodents.[133-135] Insulin appears to inhibit food intake by activating phosphatidylinositol 3-kinase (PI-3-kinase) in specific hypothalamic nuclei, a signaling pathway that is shared with leptin in its effects to reduce food intake.[136] Accordingly, reduced insulin delivery or disruption of CNS insulin signaling result in weight gain and obesity.

Insulin does, however, have well-described peripheral anabolic effects to stimulate lipid synthesis and storage. These actions of insulin, along with the idea that reactive hypoglycemia resulting from insulin responses to dietary carbohydrate is commonplace, has led to a widespread misconception that insulin causes weight gain and obesity, and to the promotion of numerous diets suggesting that weight loss can be achieved simply by avoiding foods that stimulate insulin secretion (i.e., the recent low-carbohydrate and low-glycemic-index diet fads). However, the proponents of low-carbohydrate diets do not differentiate between insulin responses to meals, when circulating insulin concentrations rapidly increase and then return to baseline levels, and chronic hyperinsulinemia secondary to $\beta$-cell adaptation to insulin resistance.

Although chronic hyperinsulinemia does appear to increase hepatic lipogenesis and may contribute to hypertriglyceridemia, as previously discussed, a direct connection between hyperinsulinemia and weight gain has not been established. It is possible that in the presence of central insulin (and leptin) resistance, the peripheral anabolic effects of insulin are unopposed and could contribute to lipogensis and weight gain. For example, this may be the case in syndromes of hypothalamic obesity, in which impaired central insulin and leptin action, combined with autonomic dysfunction driving excess insulin secretion, may contribute to the pathogenesis of obesity. Examples of this include certain animal models such as ventromedial hypothalamus or gold thioglucose-lesioned rodents[137] and humans with hypothalamic damage.[138] With regard to the glycemic index of dietary carbohydrate, Anderson et al.[139] reported that the ingestion of carbohydrates that induced larger glucose excursion and would be expected to more potently stimulate insulin secretion actually resulted in lower short-term appetite ratings and a decrease of ad libitum food intake one hour later.

Peripheral effects of hyperinsulinemia notwithstanding, little evidence directly implicates insulin responses to meals as a causal factor in weight gain and obesity. In fact, reduced insulin responses to oral and intravenous glucose and to meal ingestion have been shown to be predictive of greater future weight gain in Pima Indians[140] and of subsequent increases of visceral fat mass in Japanese Americans.[141] These data suggest that, under most conditions, insulin responses to meals are in fact protective against, rather than contributors to, weight gain and obesity. In addition, the insulin response to

meal ingestion is an important mediator of leptin production by adipose tissue (see below).

Previous studies have shown that fructose, unlike glucose, has at most weak effects to stimulate insulin secretion from pancreatic β-cells in vitro[142,143] or in vivo.[102,144] The most likely explanation for the lack of effects of fructose on insulin secretion is the low level of expression of the GLUT5 fructose transporter in β-cells.[145] Most of the small effects of ingested fructose to increase insulin is likely to result from the hepatic conversion of fructose to glucose discussed in the section on fructose metabolism and the release of the incretin hormones GIP and GLP-1.[22,146,147] A recently published study demonstrated that the integrated insulin responses to three mixed macronutrient meals consumed with fructose-sweetened beverages were reduced by about 60% compared with when the same meals were consumed with equicaloric glucose-sweetened beverages.[22] A similar persistent reduction of meal-induced insulin secretion has been observed in subjects consuming fructose-sweetened beverages with meals for 10 weeks (unpublished observation). Therefore, based on insulin's role as a component of the endocrine systems involved in long-term regulation of body weight, decreased meal-induced insulin secretion could contribute to increased energy intake and weight gain during sustained consumption of a high-fructose diet.

Glucose, independent of insulin, appears to have a direct role in regulating food intake that may not be shared by fructose. Glucose transport through brain capillaries for utilization by the CNS is mediated by GLUT3 and does not require insulin, whereas fructose does not readily cross the blood-brain barrier,[148] most likely due to the lack of GLUT5-mediated transport.[149] Since signaling in glucose-sensitive/-responsive neurons via glucose metabolism has been implicated in the regulation of food intake,[150-152] the lack of transport of fructose across the blood-brain barrier and access to these neurons could potentially contribute to dysregulation of food intake and energy balance when high levels of dietary fructose are consumed.

## Leptin

Leptin, which is produced by adipocytes, serves as a critical endocrine signal to the CNS in the regulation of food intake, energy expenditure, and body adiposity.[153] The actions of insulin and leptin to reduce food intake share a common signaling pathway via activation of PI-3-kinase.[154] Defects in the ability to produce leptin[155] or the leptin receptor[156] lead to marked hyperphagia and morbid obesity in humans. Administration of recombinant leptin reduces the appetite and produces marked weight loss in leptin-deficient patients.[157] A relative deficiency in the ability to produce leptin resulting from heterozygous mutations in the leptin gene is associated with increased body fat.[158] Circulating leptin concentrations are decreased during dieting, and the decreases are related to increased sensation of hunger in dieting women.[159]

Administration of low doses of exogenous leptin has been shown to reduce appetite in patients with low leptin levels resulting from lipodystrophy[160] and in obese subjects during an energy-restricted diet.[161] Leptin replacement also prevents the decreases of energy expenditure and thyroid axis function normally observed in humans during an energy-restricted diet.[162] Based on these observed effects, decreased leptin production during dieting and weight loss would be expected to contribute to hunger, lowered metabolic rate, and subsequent weight regain. Also of interest are clinical studies showing that low-dose leptin administration improves insulin resistance and hyperlipidemia in association with marked reductions of liver and muscle lipid deposition in subjects with low leptin levels due to lipodystrophy.[163] These effects are associated with reduced triglyceride deposition in liver and skeletal muscle.[164,165] It is now abundantly clear that leptin has a crucial role in the regulation of energy and metabolic homeostasis in humans.[166]

Although circulating leptin concentrations are highly correlated with body adiposity,[167,168] leptin levels fall during short-term fasting[169] or caloric restriction[170] to a much greater degree than would be expected from the small changes of body fat mass. Plasma leptin levels do not increase until more than 4 hours after the ingestion of a meal, indicating that leptin is not a signal directly involved in the short-term regulation of satiety, but rather that changes of leptin in response to nutritional status act in the medium- to long-term regulation of energy balance.[3,166] Circulating leptin concentrations exhibit a diurnal pattern,[171] with a mid-morning nadir and a nocturnal peak occurring between midnight and 2:00 AM. This diurnal variation is not observed in fasted subjects,[172] but is entrained by meal timing[173] and is proportional to insulin responses to meals. Insulin increases leptin gene expression and leptin secretion, and is the dominant physiological signal in the regulation of leptin production and its diurnal pattern.[153] Infusion of insulin at rates producing physiological increases of plasma insulin levels stimulates circulating leptin with a time lag of approximately 4 hours, similar to the delay in leptin production after meal ingestion.[174] The effects of insulin to increase glucose transport and oxidative glucose metabolism appear to be critical for the actions of insulin to increase leptin production by adipocytes[175-177] and for the increase of circulating leptin in response to insulin and glucose administration in humans.[178]

When human subjects consumed high-fat meals resulting in smaller postprandial glucose and insulin excursions, plasma leptin concentrations over a 24-hour period were substantially reduced and the amplitude of the diurnal leptin peak was blunted compared with low-fat/high-carbohydrate meals.[179] Decreased leptin production could contribute to the effects of high-fat diets to induce weight gain and obesity.[180-182] The ability of a low-fat/high-carbohydrate diet to maintain the amplitude of the diurnal leptin pattern was highly predictive of the loss of body weight and decreased adiposity observed in humans subjects on an ad libitum diet.[183] These data suggest that regulation of leptin production by dietary macronutrient composition has a long-term biological impact on energy homeostasis in humans.

Plasma leptin concentrations increased progressively with a time delay of about 3 to 4 hours, along with markedly elevated plasma glucose and insulin concentrations, during intravenous infusion of glucose in rhesus monkeys. In contrast, insulin secretion and leptin concentrations were not increased during infusion of the same amount of fructose.[144] In a recently published study examining the effects of fructose ingestion in humans, 12 women consumed three meals accompanied by fructose-containing beverages on one day and glucose-containing beverages on a separate day. Consumption of fructose-sweetened beverages with meals resulted in smaller postprandial glucose and insulin excursions than the consumption of beverages sweetened with glucose. Circulating leptin concentrations over 24 hours were reduced by approximately 35%, and the amplitude of the diurnal leptin pattern was blunted on the fructose day compared with the glucose day.[22] In a longer-term study, this effect persisted during 10 weeks of fructose consumption.[184] Therefore, reductions of leptin production and the amplitude of the diurnal leptin profile could lead to increased energy intake, weight gain, and obesity in individuals habitually consuming diets containing a substantial amount of energy derived from fructose.

### Ghrelin

Ghrelin is a peptide hormone primarily produced by the stomach and upper small intestine that was first identified based on its effects to stimulate growth hormone secretion.[185] Ghrelin also appears to be involved in the regulation of food intake, substrate metabolism, and body composition.[3,186] The administration of exogenous ghrelin increases food intake and, with repeated administration, reduces lipid oxidation and induces weight gain in rodents.[187,188] Hunger and ad libitum food intake are increased during intravenous ghrelin infusion in normal human subjects[189] and in patients with cancer-induced anorexia.[190] However, fasting ghrelin levels do not predict ad libitum energy intake.[191]

Circulating ghrelin levels are inversely related to body weight[187,192] and increase after diet-induced weight loss,[193,194] suggesting that increases of ghrelin after weight loss could contribute to hunger and weight regain. The increases of ghrelin after weight loss resulting from diet and exercise are not observed in patients who have lost weight after gastric by-pass surgery,[193,195] which may contribute to the high rate of success of this procedure to produce sustained weight loss. In contrast, circulating ghrelin concentrations are markedly elevated in Prader-Willi syndrome, a genetic disorder characterized by marked hyperphagia and obesity.[196,197] Plasma ghrelin concentrations decrease shortly after ingestion of a meal and remain suppressed for 2 to 3 hours thereafter. Postprandial suppression of ghrelin is blunted in obese subjects.[198] There is evidence that insulin and glucose responses to meals contribute to the suppression of ghrelin after meals.[199-201] Recent published studies demonstrated an approximately 35% decrease of plasma ghrelin levels after each of three meals accompanied by a glucose-sweetened beverage; however, postprandial suppression of ghrelin was substantially diminished when fructose-sweetened beverages were consumed with the same meals.[22] These results suggest that by failing to suppress ghrelin secretion, fructose consumption could lead to increased energy intake and weight gain.

### $PYY_{3-36}$

$PYY_{3-36}$ is a peptide hormone related to pancreatic polypeptide and neuropeptide-Y that is produced by the colon and released into the circulation in response to nutrient ingestion.[202-204] PYY administration inhibits food intake in rodents,[205,206] although this has not been reported by all investigators.[207] Because PYY does not decrease food intake in Y2 receptor knock-out mice, inhibition of food intake by PYY appears to involve binding to presynaptic Y2 receptors that inhibit neuropeptide-Y release from neurons in the arcuate nucleus of the hypothalamus. Administration of $PYY_{3-36}$ reduces appetite/hunger ratings and decreases food intake in normal-weight and obese subjects.[205,208] A relatively short-term (90-minute) infusion of $PYY_{3-36}$ produces a more prolonged reduction of appetite and food intake in humans.[205] Thus, in contrast to most gastrointestinal peptides that only inhibit short-term food intake, $PYY_{3-36}$ may function as a medium- to long-term regulator of energy intake rather than as a short-term satiety signal. The effect of fructose ingestion on the secretion and circulating levels of $PYY_{3-36}$ has not yet been reported.

## FRUCTOSE, WEIGHT GAIN, AND OBESITY

Although energy intake, body weight, and adiposity all increase in animals consuming high-fructose diets,[2] con-

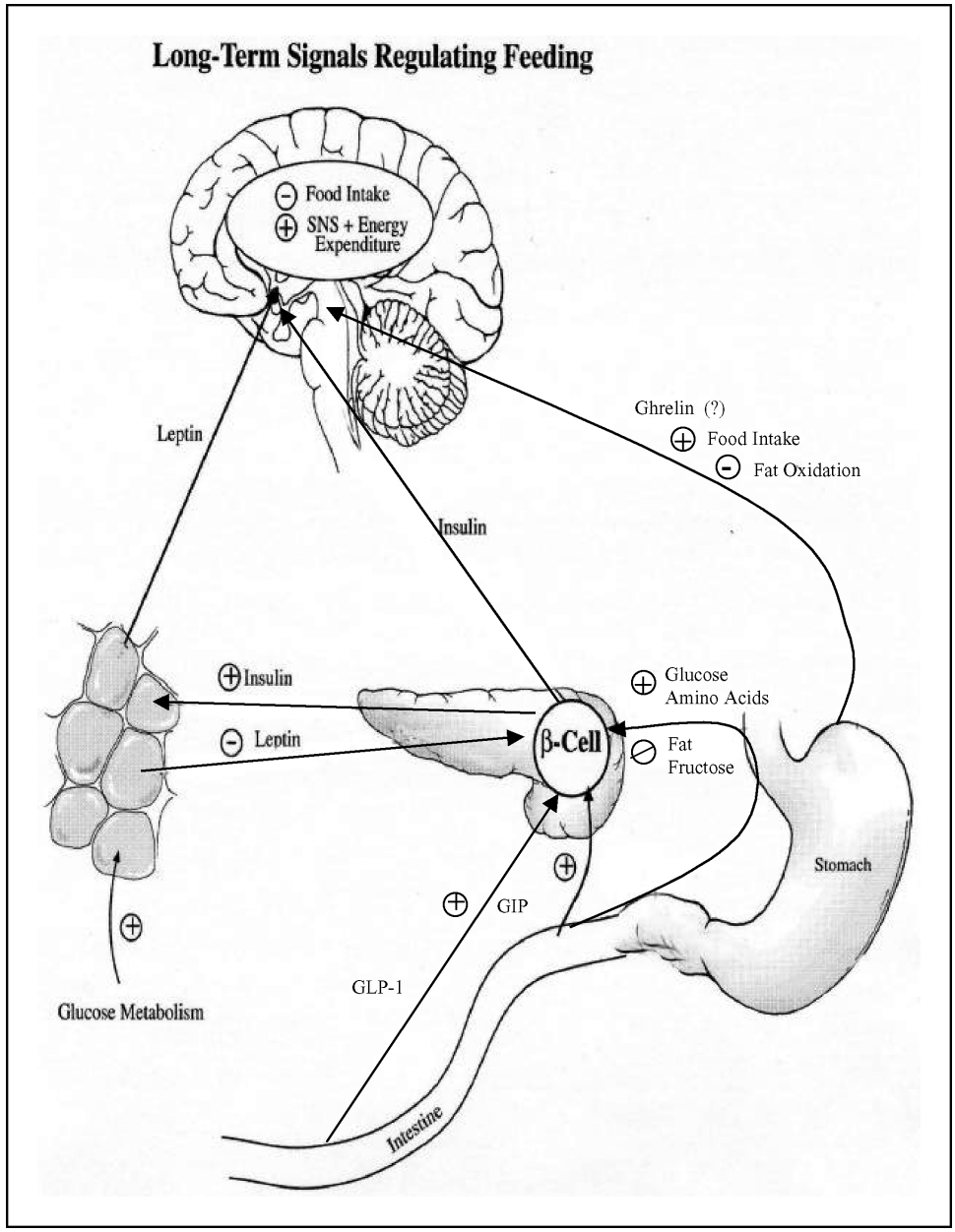


**Figure 2.** Long-term signals regulating food intake and energy homeostasis. Insulin and leptin are important long-term regulators of food intake and energy balance. Both insulin and leptin act in the CNS to inhibit food intake and to increase energy expenditure, most likely by activating the sympathetic nervous system (SNS). Insulin is secreted from the $\beta$-cells in the endocrine pancreas in response to circulating nutrients (glucose and amino acids) and to the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which are released during meal ingestion and absorption. Insulin can also act indirectly by stimulating leptin production from adipose tissue via increased glucose metabolism. In contrast, dietary fat and fructose do not stimulate insulin secretion and therefore do not increase leptin production. Ghrelin, a hormone produced by endocrine cells in the stomach, increases food intake and decreases fat oxidation and appears to have an anabolic role in long-term regulation of energy balance. Ghrelin secretion is normally suppressed after meals, but is not suppressed by fructose consumption. The long-term signals interact with the short-term signals in the regulation of energy homeostasis and appear to set sensitivity to the satiety-producing effects of short-term signals such as gastrointestinal stretch- and chemo-receptors and peptides such as cholecystokinin (CCK).

siderably less information is available from studies in humans. Epidemiological studies have implicated the intake of beverages that are high in energy from fructose with increased risk of weight gain and obesity. In data recently reported from the Nurses' Health Study, consumption of larger amounts of sugar-sweetened beverages was associated with greater weight gain and an increased risk of developing type 2 diabetes over a 9-year period in young and middle-aged women[209] Children who consume more than 265 mL (9 oz.) of carbon-

ated soft drinks per day had increased energy intake compared with those children who do not regularly consume soft drinks[210] In a longitudinal study of more than 500 schoolchildren, for each serving of sugar-sweetened beverages consumed, body mass index increased by 0.25 kg/m$^2$ and the likelihood of obesity was significantly increased.[211] A recent study conducted in the United Kingdom compared a randomized control group of 319 children aged 7 to 11 years with an intervention group of 325 children participating in a nutrition education program aimed at reducing the consumption of carbonated soft drinks. The authors reported that after 12 months, the percentage of overweight and obese children in the control group increased by 7.5%, while the proportion of overweight and obese children in the control group was unchanged.[212] A high level of consumption of sweetened beverages is particularly prevalent among Native-American children and teenagers, a population at increased risk for obesity and type 2 diabetes.[213] A 3-year intervention study that included a component aimed at reducing sweetened beverage intake lowered fasting insulin levels in Native-American high school students, suggesting a decreased risk for development of type 2 diabetes.[214]

In studies in which subjects were provided with supplemental fructose or sucrose as beverages, the subjects did not compensate for the additional energy consumed as sugars by reducing their energy intake from other sources.[215-217] One explanation for these observations could be the lack of effect of fructose ingestion on the production of hormones that have key roles in the long-term regulation of food intake and energy expenditure. As previously discussed, results of a recently published study demonstrated that ingestion of fructose-sweetened beverages with a mixed meal resulted in substantially smaller postprandial plasma glucose and insulin excursions and attenuated circulating leptin profiles compared with when glucose beverages were consumed with the same meal.[22]

The smaller postprandial excursions of circulating glucose and insulin after consumption of fructose beverages with meals may have also contributed to the observed attenuated suppression of ghrelin secretion after high-fructose meals. The decreases of insulin secretion and leptin production, along with the relative elevation of plasma ghrelin concentrations observed with fructose consumption, suggest an endocrine mechanism by which long-term fructose consumption could contribute to decreased satiety and increased food intake (Figure 2). It was also reported that consumption of fructose beverages was associated initially with increased hunger and subsequently with an increased intake of fat during ad libitum feeding the day after fructose exposure.[22] However, this effect was only observed in the subset of subjects exhibiting a psychological profile of dietary restraint that reflects a specific behavioral deportment towards food and dieting. Based on these preliminary data, further investigation of the potential interactions between behavioral traits, dietary macronutrient composition, and physiological determinants of food intake (e.g., insulin, leptin, and ghrelin) is warranted.

As discussed in detail earlier, fructose consumption, along with the intake of added sugars and total energy intake, has increased significantly over the past two to three decades. The main sources of dietary fructose are HFCS and sucrose. The lower cost of HFCS may have contributed to an increase in its use by permitting an increase in portion size of sweetened beverages without a proportionate increase in price, resulting in an increase in the total amount of fructose and the total number of calories consumed. A major issue with dietary fructose is that the endocrine profile elicited—decreased insulin secretion, a reduced diurnal leptin amplitude, and attenuated suppression of ghrelin[22]—appears more similar to that of dietary fat than that of glucose-containing carbohydrates.[179] This endocrine profile, when extrapolated to the larger population, may have facilitated an increase of total caloric intake and thereby contributed to population-based weight gain. Thus, increased fructose consumption, along with decreased physical activity and consumption of large portions of high-fat foods, may be an important contributing factor to the recent obesity epidemic. The incidence and prevalence of obesity in adults and children has increased over the same time period as the increase in fructose consumption. [218-220]

## SUMMARY

Fructose consumption, along with that of added sugars and total energy intake, has increased over the last three decades. These increases coincide with increases in the prevalence of obesity across the age spectrum. Fructose metabolism in the liver favors lipogenesis. A number of studies have shown that fructose consumption induces hyperlipidemia, particularly increases of triglycerides during the postprandial period. These effects may be exacerbated in people with the metabolic syndrome, i.e., existing hyperlipidemia and insulin resistance. The impact of fructose on insulin action is less well documented, but deserves further study. Including small to moderate amounts of fructose in the diet of patients with diabetes does not appear to be detrimental and may have favorable effects on hepatic glucose metabolism. The effects of consuming large amounts of fructose on diabetes, including the potential for worsening of hyperlipidemia and insulin resistance or contributing to weight gain and diabetic complications, is not known. The lack of effects of fructose on the known endocrine regulators

of long-term energy balance, insulin, leptin, and ghrelin, suggest that prolonged consumption of a diet high in energy from fructose would contribute, along with dietary fat and inactivity, to positive energy balance, weight gain, and obesity. There are a number of questions regarding dietary fructose and its impact on lipid and carbohydrate metabolism and energy homeostasis that need further study. These are outlined below.

### Fructose Consumption

- How much fructose is actually being consumed by the population as a whole and by specific segments of the population, particularly children and adolescents? Existing food disappearance and current survey data have limitations. New surveys should incorporate tools specifically designed to assess the consumption of fructose and fructose-containing foods.

### Fructose and Lipids

- What are the mechanisms underlying the effects of fructose to induce postprandial hypertriglyceridemia and increase ApoB levels? Are the increases primarily due to increased VLDL production, decreased clearance, or a combination of the two processes? Stable isotope studies could provide valuable new information.
- What is the impact of fructose consumption on lipid profiles in men and women with the metabolic syndrome, i.e., visceral obesity, insulin resistance, existing dyslipidemia, elevated markers of inflammation, and hypertension?
- What is the atherogenic potential of fructose-induced hyperlipidemia? In addition to increasing ApoB, does fructose have effects on lipoprotein particle size distribution (e.g., small, dense LDL) and on other cardiovascular risk factors such as plasminogen activator inhibitor-1, remnant lipoproteins, and decreased adiponectin production?

### Fructose and Insulin Resistance

- What is the impact of chronically consuming a diet high in fructose on insulin action and carbohydrate metabolism, as assessed by validated and sensitive methods such as mathematical modeling analysis of fast-sampled IV glucose tolerance test data and hyperinsulinemic clamps? Such studies are particularly important in subjects with preexisting metabolic disease such as those exhibiting components of the metabolic syndrome.
- Does consuming a high-fructose diet lead to increased levels of inflammatory markers implicated in insulin resistance and cardiovascular risk, including but not limited to C-reactive protein, tumor necrosis factor-alpha, interleukin-6, and monocyte chemoattractant protein-1, as well as markers of oxidative stress?
- Can long-term fructose consumption lead to insulin resistance by increasing lipid deposition in liver and skeletal muscle (intramyocellular lipid)?

### Fructose and Diabetes

- What levels of fructose in the diet are safe and potentially beneficial in the diet of patients with diabetes and at what level does fructose consumption have potentially detrimental effects on lipids, insulin action, $\beta$-cell function, and/or energy balance/weight gain?
- What is the impact of consuming high levels of dietary fructose on protein fructosylation, the polyol pathway, and oxidative stress, all of which could potentially contribute to the long-term complication of diabetes including retinopathy, neuropathy, and renal disease?

### Fructose and Energy Homeostasis

- Does long-term consumption of a high-fructose diet lead to increased energy intake and weight gain, and how is this related to the endocrine signals involved in the regulation of energy homeostasis?
- Does the source/formulation of dietary fructose, e.g., sucrose versus HFCS-55, influence the short-term endocrine and metabolic effects of fructose and its long-term impact on energy homeostasis?

## ACKNOWLEDGMENTS

This work was supported by Academic Network, Portland, Oregon. Academic Network receives grant funding from the Sugar Association, the Salt Institute, and Dairy Management, Inc. The author has received research funding from the International Life Science Institute (ILSI), the American Diabetes Association, The United States Department of Agriculture, and the National Institutes of Health (DK-58108 and HL-075675). The opinions expressed herein are solely those of the author and do not necessarily represent the views of Academic Network, ILSI, the American Diabetes Association, USDA, or NIH.

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